83. (New) A method of inhibiting chemokine-induced activity of hematopoietic cells at a preselected physiological site, comprising: administering to a mammal a dosage form comprising an effective amount of CRD-Cys-Leu-Asp-Pro-Lys-Gln-Lys-Trp-Ile-Gln-Cys, wherein the dosage form is linked to a site targeting moiety.

Remarks

Reconsideration and withdrawal of the rejections of the claims, in view of the remarks herein, is respectfully requested. Claims 75-83 are added. Claims 63-83 are pending.

New claims 63-83 are supported by originally-filed claims 4, 12, 17, 20, and 22, and at page 5, lines 7-12 and 22-26 of the specification.

The Examiner rejected claims 63, 65 [sic], 67, and 71 under 35 U.S.C. § 112, first paragraph, alleging that while the specification is enabling for a method of inhibiting chemokine-induced THP-1 migration by the administration of SEQ ID NO:1, 7 or 14, or CRD-Cys-Leu-Asp-Pro-Lys-Trp-Ile-Gln-Cys, the specification does not reasonably provide enablement for a method of preventing or inhibiting an indication of a chemokine-induced activity, or an indication associated with a chemokine-induced activity, by the administration of peptides. The Examiner also rejected claims 64, 66, 68-70, and 72-74 under 35 U.S.C. § 112, first paragraph, alleging that while the specification is enabling for a method of inhibiting chemokine-induced THP-1 migration by administration of SEQ ID NO:1, 7 or 14 or CRD-Cys-Leu-Asp-Pro-Lys-Trp-Ile-Gln-Cys, the specification does not reasonably provide enablement for a method of preventing or inhibiting an indication associated with hematopoietic cell recruitment, a method to enhance or increase hematopoietic cell-associated activity at a tumor site, or a method to modulate chemokine-induced activity of hematopoietic cells at a preselected physiological site. These rejections are respectfully traversed.

The bases for the rejection of claims 63, 65, 67, and 71 are that: 1) methods of prevention of an indication such as multiple sclerosis (MS) are not known to the art and the art does not recognize the nexus between the claimed method of the administration of peptides and preventing or inhibiting multiple sclerosis (citing for support to pages 1474 and 1476 of the Merck Manual of Diagnosis and Therapy, Beers and Berkov, eds., Merck Research Laboratories,

Whitehouse Station, NJ (1999)); 2) absent *in vivo* clinical data, i.e., a showing of predictability, it would require undue experimentation to practice a method of preventing or inhibiting an indication associated with a chemokine-induced activity or a method of preventing or inhibiting an indication of a chemokine-induced activity; 3) the specification provides insufficient guidance to the skilled artisan (a "medical professional" according to the Examiner) to practice the claimed methods as the specification does not provide the nexus between the etiology or treatment of MS and the claimed method nor set forth treatment regimens, including dosages, dosage forms, preferred routes of administration or dosing schedules for the disclosed peptides; 4) there are no working examples which encompass preventing or treating MS by the administration of peptides; and 5) the quantity of experimentation to practice the claimed method would be undue because the artisan would need to establish a nexus between the claimed method of administration of peptides and preventing or inhibiting MS and the skilled artisan would need to establish treatment protocols for the disclosed peptides which would entail determining preferred routes of administration, dosage forms, dosages and dosing timetables.

The bases for the rejection of claims 64, 66, 68-70, and 72-74 are that: a) the prior art teaches that the cause of myelofibrosis is unknown and so there are no art recognized methods to prevent myelofibrosis (citing to pages 900-901 of the Merck Manual of Diagnosis and Therapy); b) absent *in vivo* clinical data, it would require undue experimentation to practice the claimed methods; c) the specification provides insufficient guidance to the skilled artisan to practice the claimed methods as the specification does not provide the nexus between preventing or inhibiting a myeloproliferative disorder and the administration of the disclosed peptides and does not set forth treatment regimens, including dosages, dosage forms, preferred routes of administration or dosing schedules for the disclosed peptides; d) there are no working examples for the claimed methods which encompass myeloproliferative disorders; and e) the quantity of experimentation to practice the claimed method would be undue because the artisan would need to establish a nexus between the prevention or inhibition of a myeloproliferative disorder and the administration of the claimed peptides, and the artisan would need to establish treatment protocols for the disclosed peptides which would entail determining preferred routes of administration, dosage forms, dosages and dosing timetables.

With respect to the Examiner's assertion that the specification does not set forth dosages, dosage forms, preferred routes of administration or dosing schedules (see bases 3), 5), c) and e) of the rejections), it is Applicant's position that the selection of dosages, dosage forms, dosage schedules and routes of administration for a particular therapeutic agent is well within the skill of the art worker (see, e.g., In re Johnson, 282 F.2d 370, 127 U.S.P.Q. 216 (C.C.P.A. 1960) (the selection of suitable dosages is within the skill of the art). Applicant need not teach, and preferably omits, that which is known in the art. Hybritech Inc. v. Monoclonal Antibodies Inc., 231 U.S.P.Q. 81, 84 (Fed. Cir. 1986).

As for the nexus between the use of chemokine peptides, variants or derivatives thereof for indications associated with chemokine-induced activity (see bases 1), 3), 5), c) and e)), Applicant discloses that chemokine peptides, e.g., those corresponding to the carboxy-terminal half of a chemokine, and variants and derivatives thereof, are useful to prevent or inhibit indications associated with chemokine-induced activity, such as aberrant or pathological inflammatory processes (page 18, lines 9-10, page 30, lines 26-28, and page 98, lines 9-10 of the specification). Applicant further discloses that indications associated with chemokine-induced activity include asthma, endotoxemia and autoimmune disorders including MS (page 47, line 1 to page 50, line 14; see also page 98, line 5 to page 110, line 3).

Evidence that MS has an aberrant or pathological inflammatory component is found at page 1476 of the Merck Manual of Diagnosis and Therapy, where it is noted that certain corticosteroids (i.e., antiinflammatory agents) are the main form of therapy for MS. Moreover, the expression of certain chemokines is associated with MS (see, for example, Ransohoff et al., Cytokine Growth Factor Rev., 7, 35 (1996), and Simpson et al., J. Neuroimmunol., 84, 238 (1998), a copy of each is enclosed herewith) (see also page 104, lines 22-25 of the specification).

With respect to myelofibrosis, the Examiner is requested to consider that "fibrosis" occurs in the healing stage of inflammation (see page 707 of Churchill's Medical Dictionary, Churchill Living Stone Inc. (1989), a copy of which is enclosed herewith). In addition, the expression of PF4, a chemokine, is associated with myeloproliferative disorders (see, for instance, Wehmeier et al., Eur. J. Haematol., 45, 191 (1990) and Romano et al., Haemostatis, 20, 162 (1990), a copy of each is enclosed herewith).

Thus, there is a nexus between disorders associated with chemokine activity such as those having an aberrant or pathological inflammatory component, e.g., MS and myelofibrosis, and the use of antiinflammatory agents, e.g., chemokine peptides or variants or derivatives thereof.

In bases 1) and a) of the rejection, the Examiner questions the utility of the disclosed peptides to prevent MS or myelofibrosis. However, as MS may have a genetic component related to certain HLA allotypes (see page 1474 of the Merck Manual of Diagnosis and Therapy) and the development of myelofibrosis is associated with certain malignant diseases, infection and toxin exposure (page 900 of the Merck Manual of Diagnosis and Therapy), chemokine peptides, variants and derivatives thereof may be employed prophylactically for indications associated with chemokine-induced activity.

With respect to the "predictability or lack thereof" in bases 2) and b) of the rejection, that refers to the ability of one skilled in the art to extrapolate disclosed or known results to the claimed invention. M.P.E.P. § 2164.03. The Examiner is also reminded that data from *in vitro* or animal testing is generally sufficient to support utility, and that human clinical data is not required. M.P.E.P. § 2107.03 (clinical data is not required to satisfy the enablement requirement for pharmaceuticals and methods of medical treatment). The standard is that the evidence provided by Applicant be convincing to one of skill in the art that the disclosed agents are useful for the claimed method. In re Brandstadter, 179 U.S.P.Q. 286, 294 (C.C.P.A. 1973) and M.P.E.P. § 2164.05.

In this regard, the Examiner is respectfully requested to consider Applicant's detailed disclosure. The specification provides exemplary *in vitro* and *in vivo* assays to determine whether a particular chemokine peptide, e.g., SEQ ID NO:1, SEQ ID NO:7, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74 or SEQ ID NO:11, a variant or a derivative thereof, e.g., CRD-CLDPKQKWIQC, inhibits or reduces a chemokine-induced activity (page 50, lines 16-25). These assays include *in vitro* assays (see page 50, line 27-page 52, line 28) which detect whether an agent inhibits the chemokine-induced chemotaxis of a variety of cell types (e.g., neutrophils, monocytes, eosinophils, mast cells, platelets or lymphocytes; page 52, lines 1-2), inhibits the release of

enzymes from certain cells (such as N-acetyl-β-D-glucosamidase from monocytes or elastase from neutrophils; page 53, lines 2-13), changes the concentration of cytosolic free Ca^{2+} in various cell types (monocytes, eosinophils, neutrophils; page 53, line 15-page 54, line 18), inhibits binding to a chemokine receptor and/or displaces bound chemokine (page 54, line 20-page 55, line 27), and inhibits the co-mitogenic activity of a chemokine (page 56, lines 14-20).

Example 1 discloses the use of an *in vitro* chemotaxis assay, i.e., the inhibition of chemokine-induced THP-1 (a monocytic cell line) migration, to identify regions of human MCP-1 (hMCP1) falling within the scope of the invention, e.g., SEQ ID NO:1. Example 4 describes that a CRD peptide variant of MCP-1 inhibited MCP-1-induced THP-1 migration e.g., CRD-Cys-Leu-Asp-Pro-Lys-Trp-Ile-Gln-Cys (claims 71-74 and 81-83). Table 2 shows the inhibition by a MCP-1 chemokine peptide (SEQ ID NO:1) (claims 67-70 and 78-80) of the MCP-1-, MIP1α-, IL8- and SDF-1α-induced migration of THP-1 cells and primary human monocytes. Table 4 shows ED_{50} data for four chemokines (MCP-1, MIP1α, IL8 and SDF-1α) and selected peptides, e.g., SEQ ID NO:1, SEQ ID NO:7, and SEQ ID NO:14 (claims 63-66 and 75-77), which include variants of MCP-1 chemokine peptide, e.g., one variant peptide of human MCP-1 chemokine peptide (the variant is designated $Leu_4Ser_7Ile_{11}$peptide3(1-12)[MCP-1]) has amino acid substitutions at positions 4, 7 and 11 relative to the sequence of a 12 amino acid peptide of human MCP-1 designated peptide 3(1-12)[MCP-1], and another variant (referred to as $Ser_7Glu_8Glu_9$peptide3(1-12)[MCP-1]) has substitutions at positions 7, 8 and 9 relative to peptide 3(1-12)[MCP-1]. Thus, a particular chemokine peptide can inhibit the activity of more than one chemokine.

Table 4 also includes data from three chemokine peptides having three amino acid residues, one of which is a tripeptide from MIP-1α. Some of the peptides described in Table 4 were found to be pan-chemokine inhibitors, while others showed selectivity for certain groups of chemokines, i.e., selectivity for CC or CXC chemokines. Example 6 discloses additional experiments for tripeptides of the invention. Thus, the tripeptide WVQ, a sequence found in the carboxy-terminal half of MCP-1, MCP-3, MIP-1α, MIP-1β, RANTES, eotaxin and IL8 (see SEQ ID Nos:1, 7, 40, 42, 43, 44, and 66), inhibited all four chemokines tested, while tripeptide KQK, another sequence found in the carboxy-terminal half of MCP-1, was specific for MCP-1 (versus

MIP-1α, IL8 or SDF-1α). It is disclosed that the corresponding tripeptides for MIP-1α (SEE, see SEQ ID NO:42), SDF-1 (KLK, see SEQ ID NO:38), and IL8 (KEN, see SEQ ID NO:40) were each specific for the cognate chemokine.

It is further disclosed that the efficacy of a peptide of the invention in an animal model may be assessed by clinical parameters specific for the particular model or by general parameters such as the extent of inflammation or cellular infiltration into affected tissues (page 66, lines 15-16). For instance, in a murine endotoxemia model (Example 10), the administration of CRD-Cys-Leu-Asp-Pro-Lys-Trp-Ile-Gln-Cys (claims 71-74 and 81-83) to mice resulted in a dose-dependent decrease in serum TNF-α. In a murine asthma model (Example 11), the administration of CRD-Cys-Leu-Asp-Pro-Lys-Trp-Ile-Gln-Cys (claims 71-74 and 81-83) to mice resulted in the absence of inflammatory infiltrates in the lung (page 164, lines 15-17 and page 165, lines 18-19). Example 9 discloses the activity of CRD-Cys-Leu-Asp-Pro-Lys-Trp-Ile-Gln-Cys in a rat dermal inflammation model (see also Example 6 in PCT/US00/00821, where it is disclosed that CRD-Cys-Leu-Asp-Pro-Lys-Trp-Ile-Gln-Cys abolished MCP-1 induced recruitment of monocytes/macrophage), and PCT/US00/00821 discloses the activity of CRD-Cys-Leu-Asp-Pro-Lys-Trp-Ile-Gln-Cys in a rat ischemia/reperfusion model (i.e., the administration of CRD-Cys-Leu-Asp-Pro-Lys-Trp-Ile-Gln-Cys resulted in a complete suppression of neutrophil accumulation).

Thus, based on the extensive disclosure in Applicant's specification including the *in vitro* and *in vivo* results therein, one of ordinary skill in the art could reasonably predict that chemokine peptides, variants or derivatives thereof, would be useful for a variety of indications associated with chemokine-induced activity, e.g., indications associated with an aberrant or pathological inflammatory response.

With respect to the lack of a working embodiment for MS or myelofibrosis (bases 4) and d) of the rejection), the Examiner is respectfully reminded that it is well-settled that there is no requirement for working examples to fulfill the requirements of 35 U.S.C. § 112, first paragraph, if the invention is otherwise disclosed so that one of ordinary skill in the art can practice the invention without undue experimentation. In re Robins, 166 U.S.P.Q. 552 (C.C.P.A. 1970), In re Borokowski et al., 422 F.2d 904, 164 U.S.P.Q. 642 (C.C.P.A. 1970). M.P.E.P. § 2164.02.

As discussed above, Applicant has provided extensive *in vitro* and *in vivo* data showing that chemokine peptides, variants and derivatives thereof are useful for a variety of indications associated with chemokine-induced activity. Thus, one of ordinary skill in the art using known animal models for chronic graft rejection (chronic graft rejection is characterized by occlusive neointima and fibrosis) and for MS (i.e., experimental autoimmune encephalomyelitis) could determine, without undue experimentation, if any particular chemokine peptide or variant or derivative thereof would prevent or inhibit a chemokine-induced activity assocaited with fibrosis or MS.

Accordingly, it is respectfully submitted that the pending claims are in conformance with the requirements of 35 U.S.C. § 112, first paragraph. Therefore, withdrawal of the § 112(1) rejections of the claims is respectfully requested.

The Examiner is invited to telephone Applicant's attorney at 612-373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on this 10 day of December, 2002.

Anne M. Richards
Name

_____
Signature